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PATENT & TRADEMARK OFFICE

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28. A therapeutic composition comprising a combination a therapeutically effective amount of botulinum neurotoxin type A and botulinum neurotoxin type B.

29. A therapeutic composition comprising a combination of a therapeutically effective amount of botulinum neurotoxin type A and botulinum neurotoxin type E.

REMARKS

By way of this Amendment, claims 27-29 have been added. Accordingly, claims 1-9, and 17-29 are pending.

Support for the Claims

Support for claim 27 may be found in the specification in examples 1-6, and claim 17.

Support for claim 28 may be found in the specification at page 11, lines 22-32.

Support for claim 29 may be found in the specification at page 12, lines 21-23.

Item 2 of the Office Action - Defective Declaration

The Examiner has objected to the declaration alleging that the declaration is defective. The Examiner states that the oath or declaration is defective because the full name of each inventor

has not been set forth. Specifically, the first name of the inventor has an initial.

The requirements set forth in 37 CFR 1.63(a)(3) is to "identify each inventor by full name, including family name, and at least one given name without abbreviation together with any other given name or initial;".

Applicants respectfully submit that these requirements have been met. The declaration, as filed, states the full name of the inventors. In particular, the first named inventor, K. Roger Aoki, is identified by including his family name, "Aoki", and at least one given name without abbreviation, "Roger", together with any other given name or initial, "K". The full first name of the inventor is not required. In addition, MPEP 605.04(b) states that "J. Paul Doe" is an acceptable identification for an inventor named "John Paul Doe." Accordingly, applicants respectfully request the Examiner to withdraw the objection.

Item 3 of the Office Action - Rejections under 35 USC 112, 1st ¶

Claims 1 to 9 have been rejected under 35 USC 112, first paragraph. This is an enablement rejection. The Examiner alleges that the specification fails to provide guidance regarding a method for treating disorders and conditions claimed in the application citing In re Wands, 8 USPQ2d 1400.

Applicants have considered the Examiner's position and respectfully traverse the rejection.

The test for enablement set forth in In re Wands requires that the claimed invention be enabled so that a person of ordinary skill in the art can make and use the invention without undue experimentation. The Court stated in United States v. Telectronics, Inc., 8 USPQ2d 1217, 1223 that "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation."

The court in In re Wands discusses what constitutes undue experimentation:

> "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is undue, not experimentation ... . The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (underlining ours).

Applicants respectfully submit that the instant specification provides sufficient information to enable one of ordinary skill in the art to practice the claimed invention. One skilled in the art is a physician with several years of medical training. The relative skill of such physicians is high. Any additional experimentation that may be needed would be simply to optimize the claimed invention, and would be routine (e.g., see page 10, lines 6-19).

Applicants remind the Examiner that the specification as a whole must be used to determine whether the claims are enabled. The Examiner should not only consider specific examples. The specification discusses the state of the art, and teaches how to obtain, and or make, compositions comprising combinations of botulinum toxins (e.g., page 2, lines 24 to page 3, line 3; page 3, line 32 to page 4, line 6; page 7, lines 11-13; page 8, line 32 to page 9, line 20). In addition, the specification teaches how to use or administer such compositions (e.g., page 8, lines 21-30; page 9, line 32 to page 10, line 4; and examples 1-6). The specification also discloses how to assess whether the administration of the compositions was effective (e.g., page 11, lines 26-27; page 13, lines 20-22; page 13, lines 32-33; page 15, lines 8-9; page 16, lines 23-24; page 18, lines 7-11). Accordingly, the claims are enabled.

The Examiner seems to be requiring extraneous information that is not required to satisfy the test of enablement. For example, the Examiner states that the specification fails to provide (i) how to evaluate a patient's overall state of health; (ii) a patient's severity of condition; (iii) the amount of dosage used per patient; (iv) the length of treatment; and (v) the length of treatment and the measurement of a patient's progress. (Office Action, page 5).

In one instance, the Examiner inquires as to the "exact amount" of type A and type B toxins used in example 1. The Examiner also asks what constitutes "up to 300 units or more" in example 2.

The Examiner also is requiring that knowledge that is known to those of ordinary skill in the art be provided in the specification. For example, the Examiner seems to be requiring that a controlled study be performed on a group of patients, that a measurement of the severity of the condition to be treated be quantified, and that exact doses to treat specific conditions be disclosed. The Examiner asks, what comparison studies were performed, what was the patient population, what was the medical history of the patients and were there pre-existing medical conditions. The Examiner continues by requiring that procedures and protocols be supplied on how improvement in a patient is measured.

The Examiner further inquires, what constitutes 300 or more units, what constitutes a few hours, and what constitutes a normal position (referring to head and shoulder posture of a patient). In addition, the Examiner refers to example 3 to 3(e) asking what constitutes "substantially alleviated" and what constitutes a "therapeutic amount."

Regarding dosage, the courts have held that determining proper dosage amounts for an established treatment is routine and could be adjusted to suit the needs of an individual. (U.S. v. Telectronics, Inc. 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (1988). Therefore, applicants' respectfully submit that the specification is enabling because those skilled in the art would know how to conduct a dose response study to determine the appropriate amounts of the compositions to be used based on applicants' disclosure and the skill in the art. Such studies would not be undue.

The fact that dosages and timing of delivery of a therapeutic composition may need to be "fine tuned" for commercial uses does not indicate that claims to a method of using such a composition are "unpredictable" under the patent laws or lacking in enablement. (e.g., see Phillips Petroleum Co. V. U.S. Steel Corp., 673 F. Supp. 1278, 1291, 6 U.S.P.Q.2d 1065, 1073-1074 (1987), aff'd. 865 F.2d 1247, 9 U.S.P.Q.2d 1461 (1989)). Applicants state in the specification that the administration and dosages of the compositions in the claimed methods is to be determined by a medical professional based on the individual subject and the subject's condition (e.g., page 10, lines 6-19 of the specification).

In addition, applicants note that specific quantities or dosages are not required where the invention resides in the discovery of the activity of a composition rather than in discovering some critical range of the composition (In re Gardner et al., 166 USPQ 138 (1970); "Broad definitions of quantity or dosage are not indefinite where invention resides in finding the activity rather than in discovering some critical range or the like.").

Applicants have discovered that compositions comprising combinations of botulinum toxins are particularly useful in treating neuromuscular disorders likely due to their combined effectiveness of inhibiting neurotransmitter release. For example, the improved effectiveness may be attributed to the fact that different serotypes of botulinum toxin act on different proteins involved in exocytosis of synaptic vesicles containing neurotransmitters (e.g., see page 6, lines 28-33).

However, the instant specification includes information regarding dosages that would enable a physician to practice the claims without undue experimentation. For example, page 9, line 34 to page 10, line 5 states "[t]ypically, the dose administered to the patient may be up to about 1,000 units; for example, up to about 500 units, and preferably from about 80 to about 460 units per patient per treatment, although smaller or larger doses may be administered in appropriate circumstances." Also, as stated in the specification on page 9, lines 21 to 26, "[t]he dose of toxin administered to the patient will depend upon the severity of the condition; e.g., the number of muscle groups requiring treatment, the age and size of the patient and the potency of the toxin.

Applicants respectfully submit that the information requested by the Examiner is unnecessary for complying with the enablement requirement. All that is required is that the specification contain sufficient information to avoid undue experimentation to practice the claimed invention. To the contrary, what is known to a person skilled in the relevant art is preferably omitted from the specification (In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech v. Monoclonal Antibodies, 802 F.2d 1367); cited in MPEP § 2164.05(a)).

"A patent is a starting point and it discloses basic information by which one could practice the invention in a laboratory setting. One looks at the examples in a laboratory setting. The transformation of that invention into a product that could be commercially produced on a grand scale is not the type of

information that is normally contained in a patent...." (Syntex (U.S.A.), Inc. v. Paragon Optical, Inc., 7 U.S.P.Q.2d 1001, 1009 (1987)).

The Examiner is essentially requiring absolute certainty that the therapeutic compositions will work in a subject rather than a disclosure sufficient to provide a teaching to one of ordinary skill in order to carry out the claimed invention, as required under 35 U.S.C. § 112. "Certainty" is not mandated by the patent laws and is not desirable (In re Sichart, 196 U.S.P.Q. 209 (CCPA 1977); In re Hartop, 135 U.S.P.Q. 119 (CCPA 1967); In re Anthony, 162 U.S.P.Q. 594 (CCPA 1969)). Clinical trials and drug development require considerable economic investment. The investment is typically based on the likelihood or existence of patent protection. If applicants were forced to demonstrate the information requested by the Examiner before receiving patent protection, potential therapeutic drug candidates would never be developed because the investment would be viewed as too risky until a patent issued. This has not been, and should not be, the policy of the U.S. Patent Office.

In further support of Applicants' position, applicants enclose herewith (**Exhibit A**) as post-filing date confirmatory evidence, U.S. Patent No. 6,087,327 (the '327 patent). The '327 patent issued July 11, 2000, and has an effective filing date of June 6, 1995. Applicants' instant application has a priority date of June 10, 1993. Accordingly, the '327 patent is not prior art with respect to the instant application.

The '327 patent discloses the use of compositions comprising botulinum toxin types A and B. The data therein provides post filing date confirmatory evidence that the disclosure of the instant application enables one skilled in the art to practice the claimed invention. In particular, the '327 patent discloses that an admixture containing botulinum toxin type A and botulinum toxin type B at concentrations less than the International Units described in the instant application cause a localized denervation with effects that differ from the administration of a single toxin alone.

Based on the foregoing, Applicants respectfully submit that the instant specification contains sufficient information to enable one skilled in the art to practice the claimed invention, and accordingly, the specification is enabling.

Items 4-7 of the Office Action - Rejection under 35 USC 112, 2nd ¶

Item 4

The Examiner objects to the specification under 35 U.S.C. 112, second paragraph. The Examiner asks whether example 1 and example 1(a) represent the same experiment.

Applicants respectfully submit that the similarity of experiment 1 and experiment 1(a) is not relevant and should not be a ground for rejection. Applicants respectfully request the Examiner to withdraw the rejection.

Item 5

The Examiner has objected to the specification under 35 U.S.C. 112, second paragraph and states that claim 6 contains the trademark/trade name Dysport.

Applicants have reviewed the claims, and are unable to find a recital of the term "Dysport". Unless the Examiner can identify the use of "Dysport" with more precision, applicants respectfully request the Examiner to withdraw rejection of claim 6.

Items 6 and 7

Claims 1 to 9, and 17 to 26 have been rejected under 35 USC 112, second paragraph. In particular, the Examiner alleges the terms "therapeutically effective amount" and "therapeutic activity" are indefinite. Applicants respectfully traverse the rejection.

As a preliminary matter, applicants note that the United States Board of Patent Appeals and Interferences has already addressed the Examiner's earlier rejections of the claims regarding these terms in the parent application, U.S. Serial No. 08/075,032. At page 7, of the Decision on Appeal, the Board reversed the Examiner's rejection, and agreed with applicants that the terms "therapeutically effective amount" and "to control a duration of therapeutic activity" are definite. Thus, applicants respectfully request the Examiner to withdraw the rejections.

In addition, applicants note the meaning of these terms is made clear based on the specification in combination with the knowledge of a practitioner of ordinary skill in the field. "Therapeutically effective amount" may be used interchangeably with the term "therapeutic amount." These terms refer to amount of a composition of the invention that will provide a beneficial effect to a subject to which the composition is administered. "Therapeutic activity" is understood by a person of ordinary skill in the art to refer to a quantitative assessment of the beneficial effect provided in a specified amount of toxin.

Item 8 of the Office Action - Rejections under 35 USC 102(b)

The Examiner rejected claims 17 to 26 under 35 USC 102(b) alleging these claims are anticipated by Ciccarelli et al., "Cultural and physiological characteristics of *Clostridium botulinum* type G and the susceptibility of certain animals to its toxin", Applied and Environmental Microbiology, 34(6):843-848 (1977; referred to herein as Ciccarelli).

In particular, the Examiner alleges that Ciccarelli teaches

> "cross-neutralization tests comprising one volume of undiluted type G antitoxin mixed with five volumes of botulinum toxin types A, B, C, D, E, F and G containing 10 to 20 mouse LD_{50} /0.5 ml. The mixtures were incubated at 37°C for 30 minutes, after which 0.6 ml of each was injected into each member of a separate mouse pair. Toxins A through F were standard toxins in 50% glycerol, which are used to determine antitoxin levels in various sera" (page 844, second column; Office Action, page 8).

The Examiner apparently believes that Ciccarelli discloses a composition comprising a mixture of botulinum toxins.

Applicants have considered the rejection and respectfully traverse the rejection. Applicants respectfully submit that the Examiner has misinterpreted the Ciccarelli reference.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil of California, 2 USPQ2d 1051.

Ciccarelli does not disclose or suggest compositions comprising at least two neurotoxins selected from a group consisting of botulinum types A, B, C, D, E, F and G, as recited in the claims. In addition, Ciccarelli does not disclose or suggest compositions comprising a combination of botulinum toxin types A and B, or types A and E. Without such a disclosure, the pending claims cannot be anticipated by Ciccarelli.

Ciccarelli discloses a plurality of compositions comprising a botulinum toxin type G antitoxin and one other type of botulinum toxin. Botulinum toxin type G antitoxin is **not** a neurotoxin. Furthermore, the compositions disclosed by Ciccarelli are not therapeutic for treating neuromuscular conditions. At best, Ciccarelli discloses the following seven compositions, each of which was separately injected into each member of a separate mouse pair:

1. G antitoxin + type A toxin;
2. G antitoxin + type B toxin;
3. G antitoxin + type C toxin;
4. G antitoxin + type D toxin;
5. G antitoxin + type E toxin;
6. G antitoxin + type F toxin; and
7. G antitoxin + type G toxin (Ciccarelli, p 844, right column).

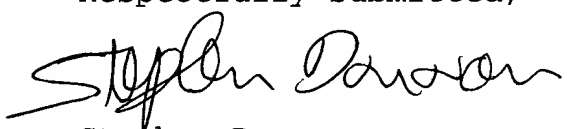
Thus, the compositions disclosed in Ciccarelli comprise one type of neurotoxin and an antitoxin. The cross neutralization tests discussed in Ciccarelli are designed to test reactivity of the type G antitoxin with each of the botulinum toxin serotypes. There is no useful information regarding treating neuromuscular disorders to be gained by mixing the antitoxins with the individual neurotoxins in the experiments disclosed by Ciccarelli.

Accordingly, applicants respectfully submit the claims are not anticipated by Ciccarelli.

In view of the above, applicants submit that the presently pending claims are in condition for allowance.

Applicants respectfully request early and favorable action in the above-identified application. Should any matters remain unresolved, the Examiner is requested to call applicants' attorney at the telephone number given below.

Respectfully submitted,



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CERTIFICATE OF EXPRESS MAIL UNDER 37 C.F.R. § 1.10

I hereby certify that this Transmittal Letter, the Response to Office Action, and the documents referred to as enclosed herein are being deposited with the United States Postal Service on this date September 27, 2001, in an envelope as "Express Mail Post Office to Addressee" Mailing Label number EL385558833US addressed to Assistant Commissioner for Patents, Washington, D.C. 20231

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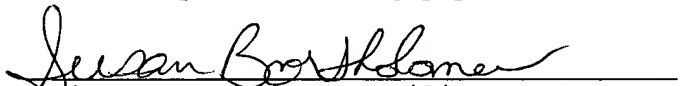
Date: September 27, 2001



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VERSION WITH MARKINGS SHOWING CHANGES MADE

The following claims have been added:

27. A therapeutic composition comprising a combination of a therapeutically effective amount of at least two neurotoxins selected from a group consisting of botulinum toxin types A, B, C, D, E, F, and G.

28. A therapeutic composition comprising a combination a therapeutically effective amount of botulinum neurotoxin type A and botulinum neurotoxin type B.

29. A therapeutic composition comprising a combination of a therapeutically effective amount of botulinum neurotoxin type A and botulinum neurotoxin type E.